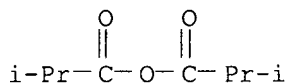


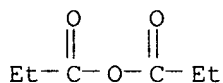
=> d ibib abs hitstr 17 1-1

L7 ANSWER 1 OF 2 HCAPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 2004:392436 HCAPLUS
 DOCUMENT NUMBER: 140:380684
 TITLE: Analogs and prodrugs of **buprenorphine**
 INVENTOR(S): Boer, Peter; **Kupper, Robert**
 PATENT ASSIGNEE(S): Euro-Celtique S.A., Luxembourg
 SOURCE: PCT Int. Appl., 23 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

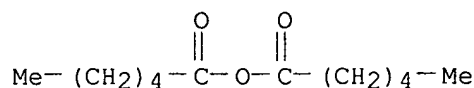
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004039317	A2	20040513	WO 2003-US33465	20031024
WO 2004039317	A3	20040923		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2004192714	A1	20040930	US 2003-692662	20031024
EP 1554290	A2	20050720	EP 2003-779164	20031024
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
PRIORITY APPLN. INFO.:			US 2002-421347P	P 20021025
			WO 2003-US33465	W 20031024
OTHER SOURCE(S): MARPAT 140:380684				
AB Disclosed are prodrugs and analogs of buprenorphine .				
IT 97-72-3, Isobutyric anhydride 123-62-6, Propionic anhydride 2051-49-2, Hexanoic anhydride 53152-21-9, Buprenorphine hydrochloride				
RL: RCT (Reactant); RACT (Reactant or reagent) (analogs and prodrugs of buprenorphine)				
RN 97-72-3 HCAPLUS				
CN Propanoic acid, 2-methyl-, anhydride (9CI) (CA INDEX NAME)				



RN 123-62-6 HCAPLUS
 CN Propanoic acid, anhydride (9CI) (CA INDEX NAME)

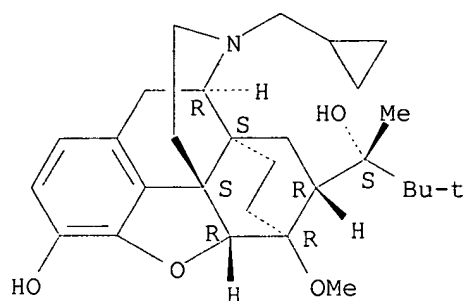


RN 2051-49-2 HCAPLUS
 CN Hexanoic acid, anhydride (9CI) (CA INDEX NAME)



RN 53152-21-9 HCAPLUS
 CN 6,14-Ethenomorphinan-7-methanol, 17-(cyclopropylmethyl)- α -(1,1-dimethylethyl)-4,5-epoxy-18,19-dihydro-3-hydroxy-6-methoxy- α -methyl-, hydrochloride, (α S,5 α ,7 α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

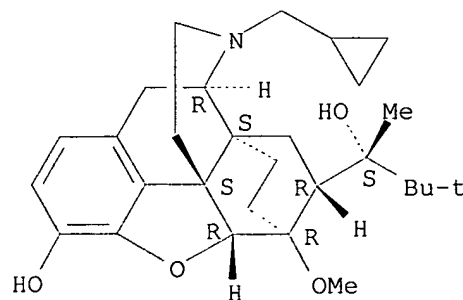


● HCl

IT **52485-79-7, Buprenorphine**
 RL: RCT (Reactant); THU (Therapeutic use); BIOL (Biological study); RACT (Reactant or reagent); USES (Uses)
 (analogs and prodrugs of **buprenorphine**)

RN 52485-79-7 HCAPLUS
 CN 6,14-Ethenomorphinan-7-methanol, 17-(cyclopropylmethyl)- α -(1,1-dimethylethyl)-4,5-epoxy-18,19-dihydro-3-hydroxy-6-methoxy- α -methyl-, (α S,5 α ,7 α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



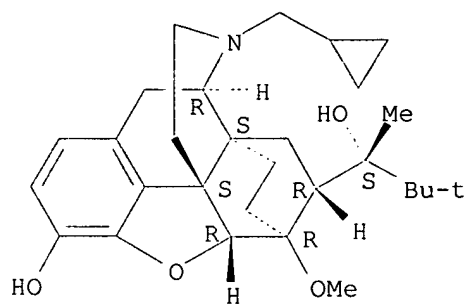
IT **52485-79-7DP, Buprenorphine, analogs**
 RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(analogues and prodrugs of **buprenorphine**)

RN 52485-79-7 HCAPLUS

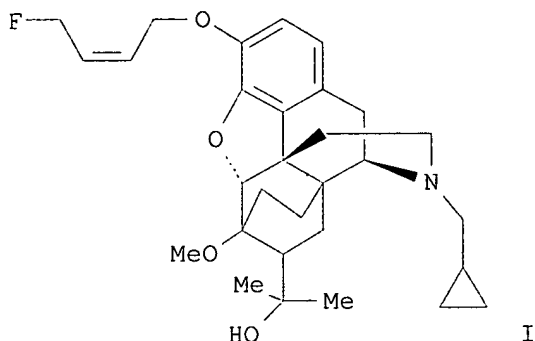
CN 6,14-Ethenomorphinan-7-methanol, 17-(cyclopropylmethyl)- α -(1,1-dimethylethyl)-4,5-epoxy-18,19-dihydro-3-hydroxy-6-methoxy- α -methyl-, (α S,5 α ,7 α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



=> d ibib abs hitstr l14 1-11

L14 ANSWER 1 OF 11 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:916747 HCAPLUS
DOCUMENT NUMBER: 137:155077
TITLE: Synthesis, NMR characterization and pharmacological
evaluation of ligands derived from diprenorphine for
central opioid receptors imaging
AUTHOR(S): Bourrel, Francois; Massou, Stephane; Baltas, Michel;
Bergon, Michel; Tafani, Mathieu; Esquere, Jean-Paul;
Tisnes, Pierre; Prigent, Yann
CORPORATE SOURCE: Laboratoire de Synthese et Physicochimie de Molecules
d'Interet Biologique, Universite Paul Sabatier, CNRS
UMR 5068, Toulouse, 31062, Fr.
SOURCE: Journal of Physical Organic Chemistry (2001
) , 14(12), 869-878
CODEN: JPOCEE; ISSN: 0894-3230
PUBLISHER: John Wiley & Sons Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 137:155077
GI



AB The aim of this work was to explore the synthesis of a tosylated derivative of diprenorphine (DPN) able to be radiolabeled with either fluorine-18 or iodine-123, making it suitable for PET or SPECT imaging studies of central opioid receptors, resp. The strategy was based on the reactivity of the C-19 alc. tertiary function. As an unexpected deacetylation of the phenolic function of the diprenorphine occurred, the prosthetic group reacted with the deprotected C-3 phenolic function instead of the C-19 alc. group. UV spectroscopy and ¹H and ¹³C NMR studies provided good evidence for the 3-phenolic substituted diprenorphine structure. Thorough 2D NMR expts. such as 1H-1H COSY, 1H-1H TOCSY, 1H-13C HMQC, 1H-13C HMBC and 1H-1H NOESY allowed us to assign fully 3-O-[(Z)-4-fluorobut-2-enyl]diprenorphine (I) and gave us an unambiguous proof of the C-3 prosthetic group position. In vitro binding studies showed low affinity for both fluoro and iodo derivs. of diprenorphine, $K_i = 0.31 \pm 0.05$ and $0.09 \pm 0.03 \mu\text{M}$, resp., for mouse brain membranes, these inhibition consts. also being in agreement with a 3-phenolic substituted structure.

IT 168131-00-8P

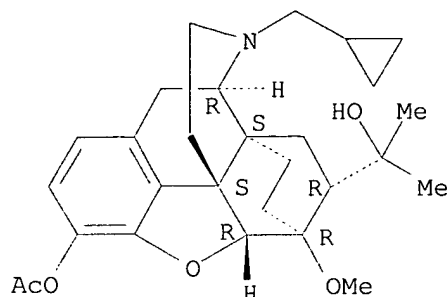
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(synthesis, NMR characterization and opioid receptor binding of
diprenorphine derivs.)

RN 168131-00-8 HCAPLUS

CN 6,14-Ethenomorphinan-7-methanol, 3-(acetyloxy)-17-(cyclopropylmethyl)-4,5-
epoxy-18,19-dihydro-6-methoxy- α,α -dimethyl-,
(5 α ,7 α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 2 OF 11 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1999:757495 HCAPLUS

DOCUMENT NUMBER: 132:58723

TITLE: Quantitative Structure-Metabolism Relationships:
Steric and Nonsteric Effects in the Enzymatic
Hydrolysis of Noncongener Carboxylic Esters

AUTHOR(S): Buchwald, Peter; Bodor, Nicholas

CORPORATE SOURCE: Center for Drug Discovery, University of Florida
Health Science Center, Gainesville, FL, 32610-0497,
USA

SOURCE: Journal of Medicinal Chemistry (1999),
42(25), 5160-5168

CODEN: JMCMAR; ISSN: 0022-2623

PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal

LANGUAGE: English

AB An attempt to quant. describe human blood in vitro hydrolysis data for
more than 80 compds. belonging to seven different noncongener series of
ester-containing drugs is presented. A parameter not yet explored in
pharmaceutical studies, the inaccessible solid angle Ω_h , calculated
around different atoms was used as a measure of steric hindrance, and the
steric hindrance around the carbonyl sp^2 oxygen ($\Omega_{hO=}$) proved the
most relevant parameter. The obtained final equation, $\log t_{1/2} = -3.805 +$
 $0.172\Omega_{hO=} - 10.146q_C + 0.112Q\log P$, also includes the AM1-calculated
charge on the carbonyl carbon (q_C) and a calculated log octanol-water
partition coefficient ($Q\log P$) as parameters and accounts for 80% of the
variability in the log half-lives of 67 compds. A number of structures are
still mispredicted, but the equation agrees very well with a recently
proposed mechanism for hydrolysis by carboxylesterases. The model, with a
predictive power tested here on three unrelated structures, should be
useful in estimating approx. rates of hydrolysis for prodrug or soft drug
candidates ahead of their synthesis.

IT 171018-29-4 171018-30-7 174586-17-5

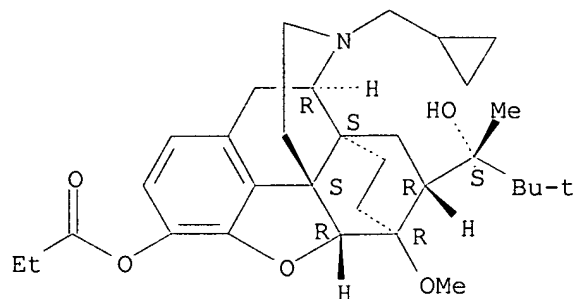
RL: BPR (Biological process); BSU (Biological study, unclassified); PRP
(Properties); BIOL (Biological study); PROC (Process)

(steric and nonsteric effects in enzymic hydrolysis of noncongener
, carboxylic esters)

RN 171018-29-4 HCAPLUS

CN 6,14-Ethenomorphinan-7-methanol, 17-(cyclopropylmethyl)- α -(1,1-dimethylethyl)-4,5-epoxy-18,19-dihydro-6-methoxy- α -methyl-3-(1-oxopropoxy)-, (α S,5 α ,7 α)- (9CI) (CA INDEX NAME)

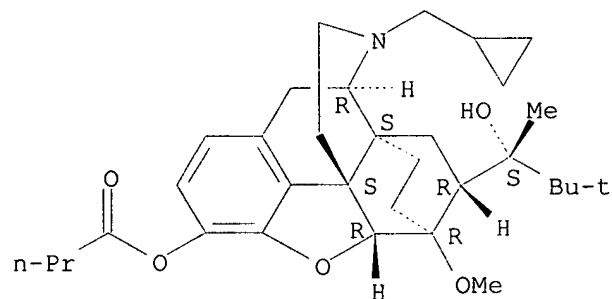
Absolute stereochemistry.



RN 171018-30-7 HCAPLUS

CN 6,14-Ethenomorphinan-7-methanol, 17-(cyclopropylmethyl)- α -(1,1-dimethylethyl)-4,5-epoxy-18,19-dihydro-6-methoxy- α -methyl-3-(1-oxobutoxy)-, (α S,5 α ,7 α)- (9CI) (CA INDEX NAME)

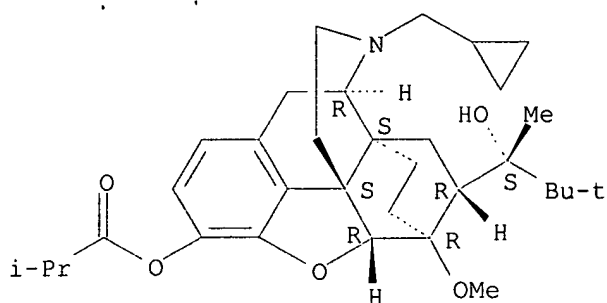
Absolute stereochemistry.



RN 174586-17-5 HCAPLUS

CN 6,14-Ethenomorphinan-7-methanol, 17-(cyclopropylmethyl)- α -(1,1-dimethylethyl)-4,5-epoxy-18,19-dihydro-6-methoxy- α -methyl-3-(2-methyl-1-oxopropoxy)-, (α S,5 α ,7 α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 105 THERE ARE 105 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE REFORMAT

L14 ANSWER 3 OF 11 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1998:26558 HCAPLUS

DOCUMENT NUMBER: 128:162492

TITLE: Subnanogram-concentration measurement of buprenorphine in human plasma by electron-capture capillary gas chromatography: application to pharmacokinetics of sublingual buprenorphine

AUTHOR(S): Everhart, E. Thomas; Cheung, Polly; Shwonek, Peter; Zabel, Karen; Tisdale, Eileen C.; Jacob, Peyton, III; Mendelson, John; Jones, Reese T.

CORPORATE SOURCE: Langley Porter Psychiatric Institute, University of California, San Francisco, CA, 94143-0984, USA

SOURCE: Clinical Chemistry (Washington, D. C.) (1997), 43(12), 2292-2302

CODEN: CLCHAU; ISSN: 0009-9147

PUBLISHER: American Association for Clinical Chemistry

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The authors describe a sensitive and specific method for the measurement of buprenorphine in human plasma. The method involves a structural analog as an internal calibrator, careful control of pH during sample extraction to maximize drug recovery, and back-extraction into acid followed by reextn. to eliminate endogenous interferences. After evaporation, sample residues are derivatized with heptafluorobutyric anhydride and analyzed by separation on a fused-silica polymethylsiloxane capillary column and electron-capture detection. Calibration curves were linear in the ranges 0.1-2.0 µg/L and 2.0-20 µg/L, with within-run CVs of 9.7% at 0.1 µg/L to 5.0% at 20 µg/L, and total CVs of 15.9% at 0.1 µg/L to 6.5% at 10 µg/L. The limit of quantification was 0.1 µg/L. The method was utilized in studies to determine the absolute bioavailability of sublingual doses of 2 mg

of

buprenorphine in 1 mL of 300 mL/L ethanol and the bioequivalence of sublingual 8-mg tablet and 300 mL/L ethanol solution formulations.

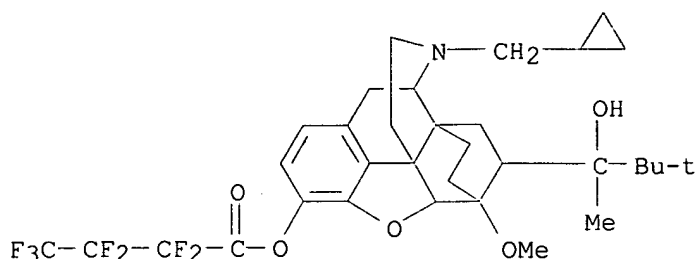
IT 206013-23-2

RL: FMU (Formation, unclassified); FORM (Formation, nonpreparative) (subnanogram-concentration measurement of buprenorphine in human plasma by electron-capture capillary gas chromatog. and application to pharmacokinetics of sublingual buprenorphine given in tablet and solution formulations)

RN 206013-23-2 HCAPLUS

CN 6,14-Ethenomorphinan-7-methanol, 17-(cyclopropylmethyl)-α-(1,1-dimethylethyl)-4,5-epoxy-3-(2,2,3,3,4,4,4-heptafluoro-1-oxobutoxy)-18,19-

dihydro-6-methoxy- α -methyl-, (α S,5 α ,7 α)- (9CI)
(CA INDEX NAME)



REFERENCE COUNT: 61 THERE ARE 61 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 4 OF 11 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1997:742522 HCAPLUS

DOCUMENT NUMBER: 128:85891

TITLE: Synthesis of opioid receptor imaging agent
7 α -O-IA-DPN

AUTHOR(S): Wang, Rongfu; Tafani, J. A. M.; Bergon, M.; Guirand, R.

CORPORATE SOURCE: First Hosp. Beijing Medical Univ., Beijing, 100034, Peop. Rep. China

SOURCE: Zhonghua Heyixue Zazhi (1997), 17(1), 23-25
CODEN: CITCDE; ISSN: 0253-9780

PUBLISHER: Jiangsusheng Yuanzi Yixue Yanjiuso

DOCUMENT TYPE: Journal

LANGUAGE: Chinese

AB 7 α -O-iodoallyl diprenorphine (7 α -O-IA-DPN) was obtained in one step by radioiododestannylation, which included selection of DPN as an opioid antagonist, regioselective protection of the DPN phenol tertiary-OH using acetylation, and introduction of vinyl stannane as prosthetic group into the tertiary alc. group position in the 7 α -side chain. The iodinated DPN derivative showed high radiolabeled yield (>90%) with 80 TBq/mmol specific radioactivity and >95% radiochem. purity. In vitro opioid receptor binding anal. showed very high affinity (K_i = 0.4 nmol L⁻¹).

IT 168131-00-8P, 3-Acetyl diprenorphine

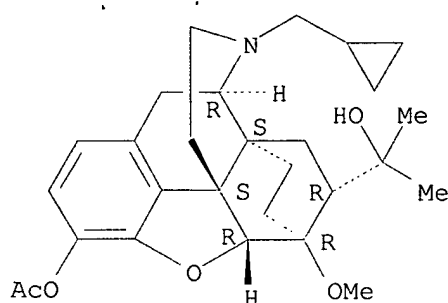
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(synthesis of opioid receptor imaging agent 7-O-iodoallyl diprenorphine)

RN 168131-00-8 HCAPLUS

CN 6,14-Ethenomorphinan-7-methanol, 3-(acetyloxy)-17-(cyclopropylmethyl)-4,5-epoxy-18,19-dihydro-6-methoxy- α , α -dimethyl-,
(5 α ,7 α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L14 ANSWER 5 OF 11 HCAPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 1996:653389 HCAPLUS
 DOCUMENT NUMBER: 125:301302
 TITLE: Method of manufacturing buprenorphine
 INVENTOR(S): Stelmach, Piotr; Bobrowska, Ewa; Falek, Krzysztof
 PATENT ASSIGNEE(S): Warszawskie Zaklady Farmaceutyczne Polfa, Pol.
 SOURCE: Pol., 4 pp.
 CODEN: POXXA7
 DOCUMENT TYPE: Patent
 LANGUAGE: Polish
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PL 166095	B1	19950331	PL 1991-289716	19910403 <--
PRIORITY APPLN. INFO.:			PL 1991-289716	19910403 <--
OTHER SOURCE(S):	CASREACT 125:301302			
GI				

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Buprenorphine I.HCl, useful as analgesic (no data), was prepared by acylation of compound II with cyclopropanecarbonyl chloride in the presence of Et₃N in CHCl₃ at 0-5° followed by reduction of the intermediate III with LiAlH₄ in THF.

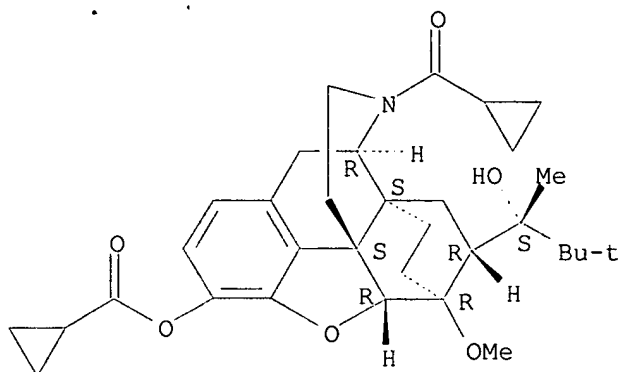
IT **182693-14-7P**

RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
 (method of manufacturing buprenorphine)

RN 182693-14-7 HCAPLUS

CN 6,14-Ethenomorphinan-7-methanol, 17-(cyclopropylcarbonyl)-3-[(cyclopropylcarbonyl)oxy]-α-(1,1-dimethylethyl)-4,5-epoxy-18,19-dihydro-6-methoxy-α-methyl-, [5α,7α(S)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L14 ANSWER 6 OF 11 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1996:648717 HCAPLUS

DOCUMENT NUMBER: 125:316126

TITLE: Permeation of buprenorphine and its 3-alkyl-ester prodrugs through human skin

AUTHOR(S): Stinchcomb, Audra L.; Paliwal, Anupam; Dua, Rajesh; Imoto, Hirofumi; Woodard, Ronald W.; Flynn, Gordon L.

CORPORATE SOURCE: College Pharmacy, University Michigan, Ann Arbor, MI, 48109, USA

SOURCE: Pharmaceutical Research (1996), 13(10), 1519-1523

CODEN: PHREEB; ISSN: 0724-8741

PUBLISHER: Plenum

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Homologous 3-alkyl-ester prodrugs (C2 to C4) of buprenorphine with decreased crystallinity have been synthesized and evaluated for transdermal delivery commensurate with opioid dependence treatment. To assess the influence of derivatization on delivery, the permeation of the prodrugs through human skin was determined in vitro. Prodrug metabolism was measured in human blood and skin supernatant in vitro along with chemical hydrolysis controls. The prodrugs' octanol/water partition coeffs. were measured. Without exception, the prodrugs were completely hydrolyzed on passing through the skin and appeared as buprenorphine in the receptor compartment. However, using saturation conditions, in no instance did the buprenorphine flux through skin from a prodrug solution exceed the flux of buprenorphine base itself in vitro. Moreover, the flux of the acetyl ester, the least hydrophobic of the prodrugs, was not significantly elevated upon stripping the skin. Whether in blood or the skin supernatant, the prodrugs hydrolyzed in an apparent first-order fashion and rate consts. and half-lives were calculated. We conclude from the results that the prodrugs' very high octanol/water partition coeffs. (hydrophobicity) placed them in viable tissue layer controlled diffusion. Moreover, the flux of the acetyl ester, the least hydrophobic of the prodrugs, was not significantly elevated upon stripping the skin. Whether in blood or the skin supernatant, the prodrugs hydrolyzed in an apparent first-order fashion and rate consts. and half-lives were calculated. We conclude from the results that the prodrugs' very high octanol/water partition coeffs. (hydrophobicity) placed them in viable tissue layer controlled diffusion. Consequently, one does not derive the potential flux-increasing benefit of reducing crystallinity that was expected.

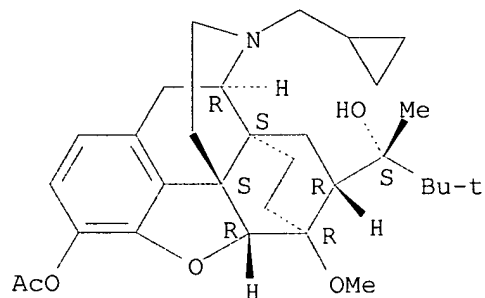
IT 171018-28-3 171018-29-4 171018-30-7
174586-17-5

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(permeation of buprenorphine and its 3-alkyl-ester prodrugs through human skin)

RN 171018-28-3 HCAPLUS

CN 6,14-Ethenomorphinan-7-methanol, 3-(acetyloxy)-17-(cyclopropylmethyl)- α -(1,1-dimethylethyl)-4,5-epoxy-18,19-dihydro-6-methoxy- α -methyl-, [5 α ,7 α (S)]- (9CI) (CA INDEX NAME)

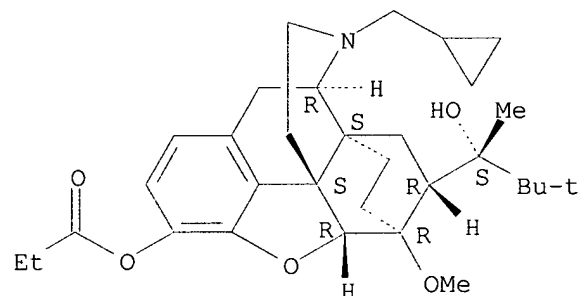
Absolute stereochemistry.



RN 171018-29-4 HCAPLUS

CN 6,14-Ethenomorphinan-7-methanol, 17-(cyclopropylmethyl)- α -(1,1-dimethylethyl)-4,5-epoxy-18,19-dihydro-6-methoxy- α -methyl-3-(1-oxopropoxy)-, (α S,5 α ,7 α)- (9CI) (CA INDEX NAME)

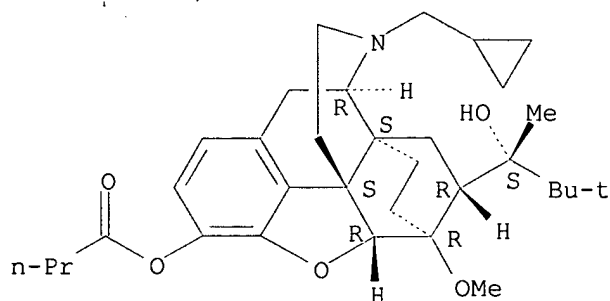
Absolute stereochemistry.



RN 171018-30-7 HCAPLUS

CN 6,14-Ethenomorphinan-7-methanol, 17-(cyclopropylmethyl)- α -(1,1-dimethylethyl)-4,5-epoxy-18,19-dihydro-6-methoxy- α -methyl-3-(1-oxobutoxy)-, (α S,5 α ,7 α)- (9CI) (CA INDEX NAME)

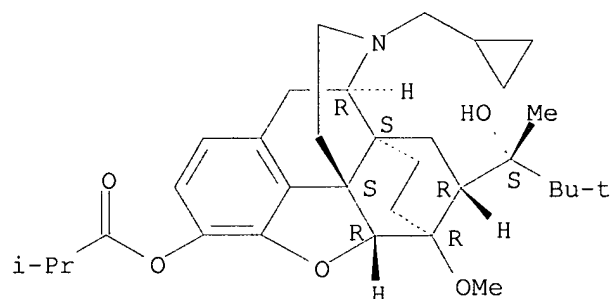
Absolute stereochemistry.



RN 174586-17-5 HCAPLUS

CN 6,14-Ethenomorphinan-7-methanol, 17-(cyclopropylmethyl)- α -(1,1-dimethylethyl)-4,5-epoxy-18,19-dihydro-6-methoxy- α -methyl-3-(2-methyl-1-oxopropoxy)-, (α S,5 α ,7 α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L14 ANSWER 7 OF 11 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1996:444785 HCAPLUS

DOCUMENT NUMBER: 125:157614

TITLE: Simultaneous assay of buprenorphine and norbuprenorphine by negative chemical ionization tandem mass spectrometry

AUTHOR(S): Kuhlman, James J., Jr.; Magluilo, Joseph, Jr.; Cone, Edward; Levine, Barry

CORPORATE SOURCE: Division Forensic Toxicology, Armed Forces Institute Pathology, Washington, DC, USA

SOURCE: Journal of Analytical Toxicology (1996), 20(4), 229-235

CODEN: JATOD3; ISSN: 0146-4760

PUBLISHER: Preston Publications

DOCUMENT TYPE: Journal

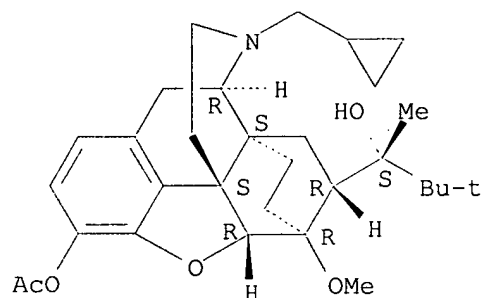
LANGUAGE: English

AB A method for the simultaneous measurement of buprenorphine and its N-dealkylated metabolite, norbuprenorphine, in human plasma was developed with neg. chemical ionization tandem mass spectrometry. Buprenorphine and norbuprenorphine were extracted from biol. fluids by solid-phase extraction

The samples were derivatized with heptafluorobutyric anhydride and measured with neg. chemical ionization tandem mass spectrometry. Buprenorphine formed a heptafluorobutyryl derivative and norbuprenorphine formed a

- AB In vitro skin permeation of buprenorphine (BUP) and three of its alkyl ester prodrugs was evaluated using hairless mouse skin. The 3 esters selected were the acetyl ester (Ac-BUP), Bu ester (Bu-BUP), and iso-Bu ester (Isb-BUP). These drugs were applied on the skin as saturated slurries in 3 vehicles commonly used to formulate agents for transdermal purposes: propylene glycol, polyethylene glycol 400 (PEG 400), and light mineral oil. Unique solubilities were found for each drug on each vehicle. Fluxes through hairless mouse skin were evaluated for each combination of drug and vehicle using Franz diffusion cells. From PEG 400 formulations, the skin fluxes of BUP, Ac-BUP, Bu-BUP, and Isb-BUP were 0.47, 1.64, 0.33, 0.75 $\mu\text{g}/\text{cm}^2/\text{h}$, resp. Thus, among the 3 potential prodrugs chosen, only Ac-BUP showed significantly higher skin fluxes than BUP. There were no inter-vehicle differences in the fluxes from saturated slurries between the vehicles. Moreover, all the esters were detected substantially in the form of regenerated parent drug (BUP) in the receptor compartment. Indeed, only Ac-BUP exited the skin in a measurably intact form, but the fraction escaping metabolism in transit was small (approx. 2%). However, based on drug dispositions in the skin, the regeneration of buprenorphine seems to depend on the alkyl chain length of the ester moiety. The molar percentages of regenerated parent drug in whole drug collected from the skin following the permeation expts. were: Ac-BUP, 9.2%; Bu-BUP, 40.7%; Isb-BUP, 9.6%, resp. Thus, only Ac-BUP appears promising as a prodrug of buprenorphine, because it is not overly hydrophilic for skin permeation and is also highly metabolized to the parent compound while in the skin.
- IT **171018-28-3**, Buprenorphine 3-acetate **171018-30-7**, Buprenorphine 3-butanoate **174586-17-5**
 RL: BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses) (vehicle effects on permeation of buprenorphine and its alkyl esters through skin)
- RN **171018-28-3** HCAPLUS
 CN 6,14-Ethenomorphinan-7-methanol, 3-(acetyloxy)-17-(cyclopropylmethyl)- α -(1,1-dimethylethyl)-4,5-epoxy-18,19-dihydro-6-methoxy- α -methyl-, [5 α ,7 α (S)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



- RN **171018-30-7** HCAPLUS
 CN 6,14-Ethenomorphinan-7-methanol, 17-(cyclopropylmethyl)- α -(1,1-dimethylethyl)-4,5-epoxy-18,19-dihydro-6-methoxy- α -methyl-3-(1-oxobutoxy)-, (α S,5 α ,7 α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

bis-heptafluorobutyryl derivative; consequently, the sensitivity of norbuprenorphine was substantially higher than buprenorphine. The limit of quantitation (LOQ) for buprenorphine was 0.20 ng/mL, and the LOQ for norbuprenorphine was 0.03 ng/mL. Daily calibration curves were prepared. Buprenorphine was linear from 0.15 ng/mL to 20 ng/mL, and norbuprenorphine was linear between 0.016 ng/mL and 5 ng/mL. Between-run and within-run precision for buprenorphine at 0.5 ng/mL were 13.8% and 9.8%, resp. Between-run and within-run precision for norbuprenorphine at 0.5 ng/mL were 23.1% and 17.9%, resp. The mol. anion for buprenorphine was used as a precursor ion, whereas the [M-197]⁻ was used as a precursor ion for norbuprenorphine in tandem mass spectrometry. Product ion spectra from collision-induced dissociation resulted principally from dissociations of the heptafluorobutyryl group. Monitoring select precursor to product ion reactions and using qualifier ion ratios increased the method's sensitivity and selectivity. The method was applied to samples collected from a patient who received oral and s.c. buprenorphine. Buprenorphine plasma concns. ranged from less than 0.20 ng/mL to 8.7 ng/mL.

IT 180338-85-6

RL: ANT (Analyte); ANST (Analytical study)

(buprenorphine and norbuprenorphine simultaneous determination by neg.

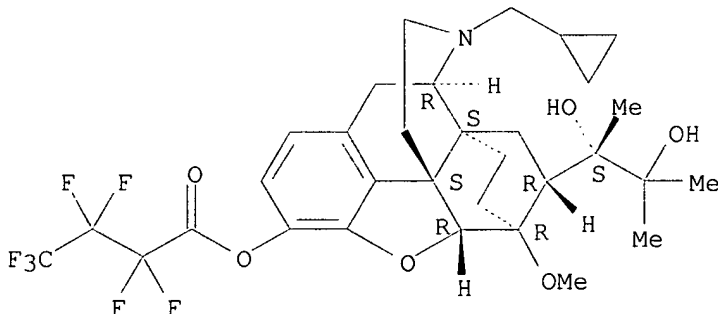
chemical

ionization tandem mass spectrometry)

RN 180338-85-6 HCAPLUS

CN 6,14-Ethenomorphinan-7-methanol, 17-(cyclopropylmethyl)-4,5-epoxy-3-(2,2,3,3,4,4,4-heptafluoro-1-oxobutoxy)-18,19-dihydro- α -(1-hydroxy-1-methylethyl)-6-methoxy- α -methyl-, [5 α ,7 α (S)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L14 ANSWER 8 OF 11 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1996:127303 HCAPLUS

DOCUMENT NUMBER: 124:211800

TITLE: Transdermal prodrug concepts: permeation of buprenorphine and its alkyl esters through hairless mouse skin and influence of vehicles

AUTHOR(S): Imoto, Hirofumi; Zhou, ZiQi; Stinchcomb, Audra L.; Flynn, Gordon L.

CORPORATE SOURCE: Coll. Pharmacy, Univ. Michigan, Ann Arbor, MI, 48109-1065, USA

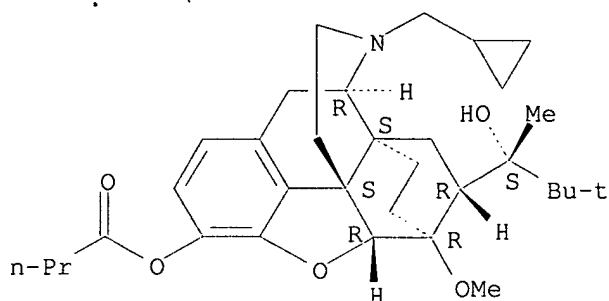
SOURCE: Biological & Pharmaceutical Bulletin (1996), 19(2), 263-7

CODEN: BPBLEO; ISSN: 0918-6158

PUBLISHER: Pharmaceutical Society of Japan

DOCUMENT TYPE: Journal

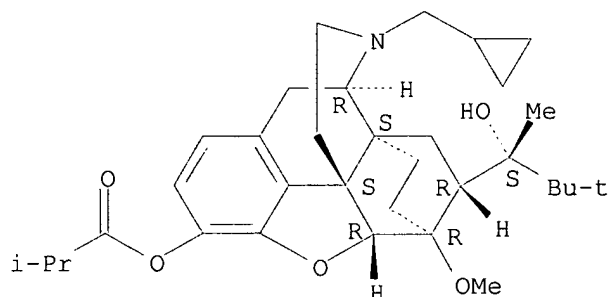
LANGUAGE: English



RN 174586-17-5 HCAPLUS

CN 6,14-Ethenomorphinan-7-methanol, 17-(cyclopropylmethyl)- α -(1,1-dimethylethyl)-4,5-epoxy-18,19-dihydro-6-methoxy- α -methyl-3-(2-methyl-1-oxopropoxy)-, (α S,5 α ,7 α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L14 ANSWER 9 OF 11 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1995:873901 HCAPLUS

DOCUMENT NUMBER: 123:350075

TITLE: A solubility and related physicochemical property comparison of buprenorphine and its 3-alkyl esters
 AUTHOR(S): Stinchcomb, Audra L.; Dua, Rajesh; Paliwal, Anupam; Woodard, Ronald W.; Flynn, Gordon L.

CORPORATE SOURCE: College of Pharmacy, The University of Michigan, Ann Arbor, MI, 48109-1065, USA

SOURCE: Pharmaceutical Research (1995), 12(10), 1526-9

CODEN: PHREEB; ISSN: 0724-8741

PUBLISHER: Plenum

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Modification of buprenorphine with an alkyl ester moiety accomplishes the physicochem. task required to improve its flux across a lipid membrane, as long as the diffusion coefficient of the drug has not been decreased and the mol. mechanism of permeation remains the same. The ethers can be potential prodrugs for buprenorphine.

IT 171018-28-3 171018-29-4 171018-30-7

171018-31-8 171018-32-9 171018-33-0

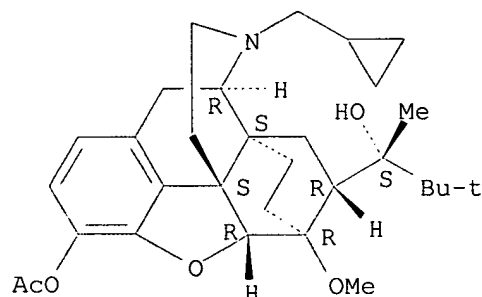
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(solubility and related physicochem. properties of buprenorphine and its 3-alkyl esters)

RN 171018-28-3 HCAPLUS

CN 6,14-Ethenomorphinan-7-methanol, 3-(acetyloxy)-17-(cyclopropylmethyl)- α -(1,1-dimethylethyl)-4,5-epoxy-18,19-dihydro-6-methoxy- α -methyl-, [5 α ,7 α (S)]- (9CI) (CA INDEX NAME)

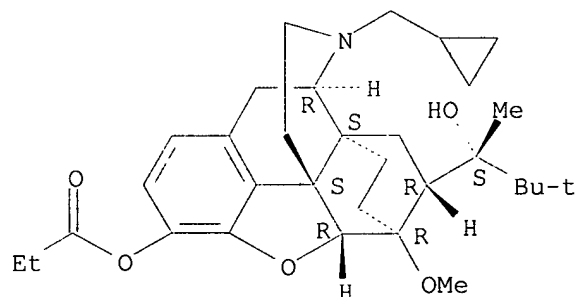
Absolute stereochemistry.



RN 171018-29-4 HCAPLUS

CN 6,14-Ethenomorphinan-7-methanol, 17-(cyclopropylmethyl)- α -(1,1-dimethylethyl)-4,5-epoxy-18,19-dihydro-6-methoxy- α -methyl-3-(1-oxopropoxy)-, (α S,5 α ,7 α)- (9CI) (CA INDEX NAME)

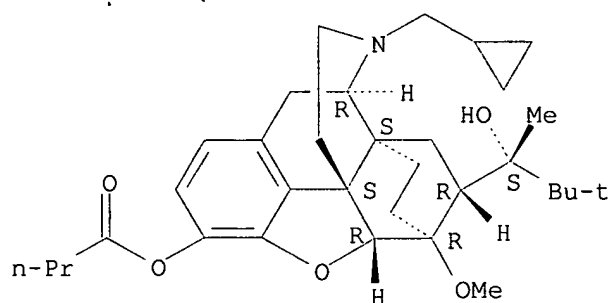
Absolute stereochemistry.



RN 171018-30-7 HCAPLUS

CN 6,14-Ethenomorphinan-7-methanol, 17-(cyclopropylmethyl)- α -(1,1-dimethylethyl)-4,5-epoxy-18,19-dihydro-6-methoxy- α -methyl-3-(1-oxobutoxy)-, (α S,5 α ,7 α)- (9CI) (CA INDEX NAME)

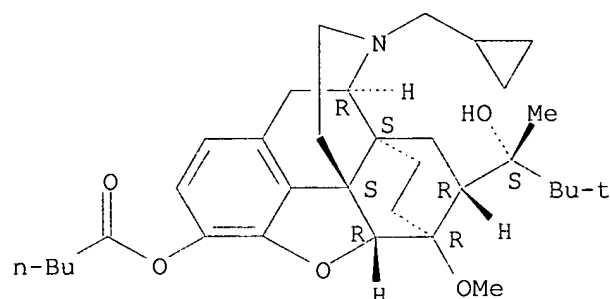
Absolute stereochemistry.



RN 171018-31-8 HCAPLUS

CN 6,14-Ethenomorphinan-7-methanol, 17-(cyclopropylmethyl)- α -(1,1-dimethylethyl)-4,5-epoxy-18,19-dihydro-6-methoxy- α -methyl-3-[(1-oxopentyl)oxy]-, [5 α ,7 α (S)]- (9CI) (CA INDEX NAME)

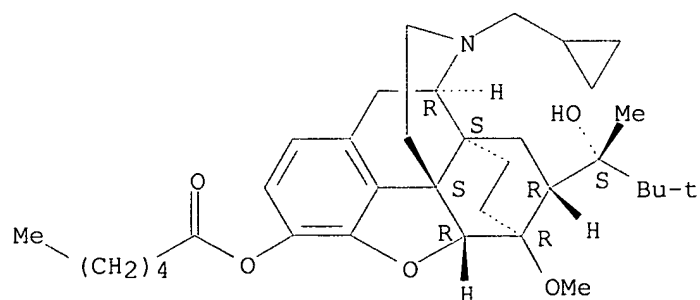
Absolute stereochemistry.



RN 171018-32-9 HCAPLUS

CN 6,14-Ethenomorphinan-7-methanol, 17-(cyclopropylmethyl)- α -(1,1-dimethylethyl)-4,5-epoxy-18,19-dihydro-6-methoxy- α -methyl-3-[(1-oxohexyl)oxy]-, [5 α ,7 α (S)]- (9CI) (CA INDEX NAME)

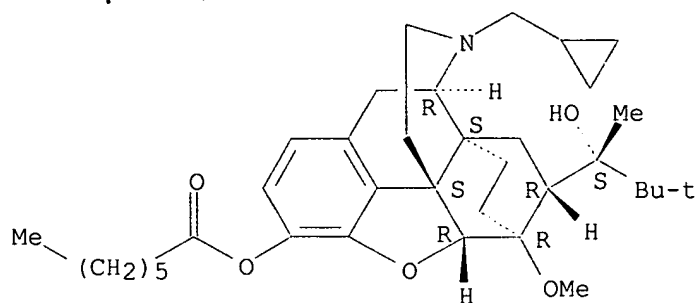
Absolute stereochemistry.



RN 171018-33-0 HCAPLUS

CN 6,14-Ethenomorphinan-7-methanol, 17-(cyclopropylmethyl)- α -(1,1-dimethylethyl)-4,5-epoxy-18,19-dihydro-6-methoxy- α -methyl-3-[(1-oxoheptyl)oxy]-, (α S,5 α ,7 α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L14 ANSWER 10 OF 11 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1995:701521 HCAPLUS

DOCUMENT NUMBER: 123:228580

TITLE: Synthesis and characterization of 7α-O-iodoallyl diprenorphine: a new ligand for potential SPECT imaging of opioid receptors

AUTHOR(S): Wang, R. F.; Tafani, J. A. M.; Bergon, M.; Tisnes, P.; Coulais, Y.; Zajac, J. M.; Guiraud, R.

CORPORATE SOURCE: Fac. Medecine, Toulouse, 31077, Fr.

SOURCE: Journal of Labelled Compounds & Radiopharmaceuticals (1995), 36(7), 611-23

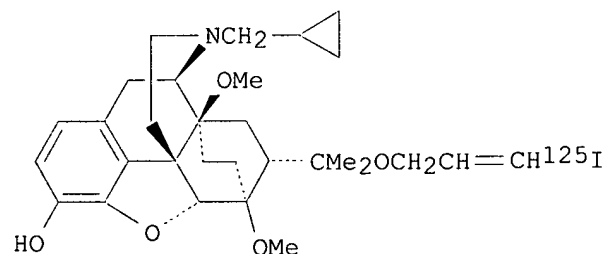
CODEN: JLCRD4; ISSN: 0362-4803

PUBLISHER: Wiley

DOCUMENT TYPE: Journal

LANGUAGE: English

GI



I

AB The preparation and synthesis of [125I]7α-O-iodoallyldiprenorphine (I) a high affinity opioid receptor antagonist, is described using a versatile vinylstannane as prosthetic group for radioiodination at the tertiary alc. group in the 7α-side chain. Radioiododestannylation with selective conditions in one step occurs under mild, no-carrier-added-conditions to give the corresponding [125I]7α-O-iodoallyl diprenorphine analog in good radiolabeled yields (70-90%) with specific radioactivity 80 TBq/mmol (2200 Ci/mmol) and radiochem. purity >95%. Iodoallyl diprenorphine exhibited in vitro a very high affinity ($K_i = 0.4$ nM), so that this radioligand could be suitable for imaging opioid receptors in living humans by Single Photon Emission Computed Tomog. (SPECT).

IT 168131-00-8P, 3-Acetyldiprenorphine

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

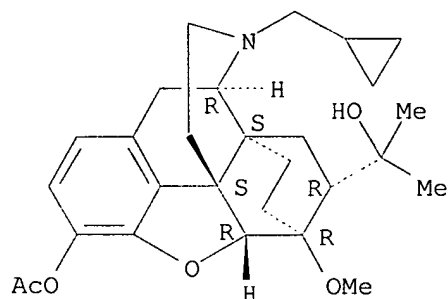
(synthesis and characterization of iodoallyldiprenorphine a new ligand

for potential SPECT imaging of opioid receptors)

RN 168131-00-8 HCAPLUS

CN 6,14-Ethenomorphinan-7-methanol, 3-(acetyloxy)-17-(cyclopropylmethyl)-4,5-epoxy-18,19-dihydro-6-methoxy- α,α -dimethyl-, (5 α ,7 α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L14 ANSWER 11 OF 11 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1985:608220 HCAPLUS

DOCUMENT NUMBER: 103:208220

TITLE: Dual mass spectrometry of trifluoroacetyl derivatives of opioid bases

AUTHOR(S): Yashiki, Mikio; West, Fanny B.; Brandenberger, Hans

CORPORATE SOURCE: Sch. Med., Hiroshima Univ., Hiroshima, 734, Japan

SOURCE: GC-MS News (1985), 13(4), 101-6

CODEN: GMNEDS; ISSN: 0388-1288

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The mass spectra of 11 trifluoroacetyl (TFA) derivs. of opioid bases were recorded quasi-simultaneously by pos. electron impact mass spectrometry and neg. chemical ionization mass spectrometry at low reagent gas pressure (electron attachment, reagent gas CH₄ at 3 + 10⁻³ torr). The derivatization was accomplished either by injecting the free base together with N-methyl-bis-trifluoroacetamide directly in the gas chromatog. (GC), or by preheating the free base together with MBTFA at 220°. All TFA derivs. except for the hydromorphone, naloxone and apomorphine derivative yielded m/z 113, the CF₃COO⁻ residue, as base anion. With hydromorphone and naloxone, 2 and 3 TFA groups resp. were introduced into the mol. For all derivs., the neg. total ion current (TIC) was stronger than the pos. TIC. The derivs. showed better chromatog. properties than the parent compds. The detection levels of derivs. determined by GC with electron capture detector and GC with neg. ion detection were similar. Morphine [57-27-2] in urine of a drug addict was identified by using the proposed method.

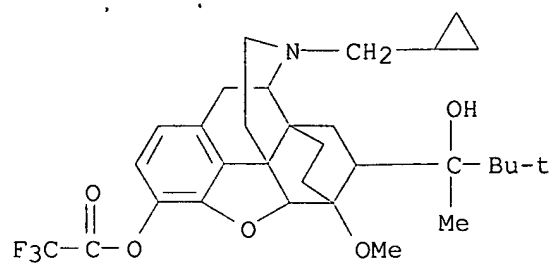
IT 99318-72-6

RL: PRP (Properties)

(mass spectra of)

RN 99318-72-6 HCAPLUS

CN 6,14-Ethenomorphinan-7-methanol, 17-(cyclopropylmethyl)- α -(1,1-dimethylethyl)-4,5-epoxy-18,19-dihydro-6-methoxy- α -methyl-3-[(trifluoroacetyl)oxy]-, [5 α ,7 α (S)]- (9CI) (CA INDEX NAME)



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(FILE 'HOME' ENTERED AT 12:13:13 ON 09 FEB 2006)

FILE 'HCAPLUS' ENTERED AT 12:13:23 ON 09 FEB 2006

L1 E BOER F PETER/AU
77 SEA ABB=ON ("BOER F P"/AU OR "BOER F PETER"/AU OR "BOER FRANK
PETER"/AU)
E KUPPER ROBERT/AU
L2 35 SEA ABB=ON ("KUPPER ROBERT"/AU OR "KUPPER ROBERT J"/AU OR
"KUPPER ROBERT JOE"/AU)
L3 0 SEA ABB=ON L1 AND L2
L4 112 SEA ABB=ON L1 OR L2
L5 2 SEA ABB=ON L4 AND ?BUPRENORPHINE?
SELECT RN L5 1-1

FILE 'REGISTRY' ENTERED AT 12:15:44 ON 09 FEB 2006

L6 5 SEA ABB=ON (52485-79-7/BI OR 123-62-6/BI OR 2051-49-2/BI OR
53152-21-9/BI OR 97-72-3/BI)

FILE 'HCAPLUS' ENTERED AT 12:16:01 ON 09 FEB 2006

L7 2 SEA ABB=ON L5 AND L6
L8 ANALYZE L7 1-1 CT : 2 TERMS

FILE 'REGISTRY' ENTERED AT 12:25:13 ON 09 FEB 2006

L9 1 SEA ABB=ON BUPRENORPHINE/CN
L10 STRUCTURE 52485-79-7
L11 2 SEA SSS SAM L10
L12 18 SEA SSS FUL L10

*18 compds. from Registry - see "d que stat"
for structure (attached)*

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L13 15 SEA ABB=ON L12
L14 11 SEA ABB=ON L13 AND (PRD<20021025 OR PD<20021025)

11 cit's in CAPLUS

FILE 'USPATFULL' ENTERED AT 12:31:00 ON 09 FEB 2006

L15 0 SEA ABB=ON L13 AND (PRD<20021025 OR PD<20021025)

0 cit's in USPatfull

FILE HOME

FILE HCAPLUS

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* The CA roles and document type information have been removed from *
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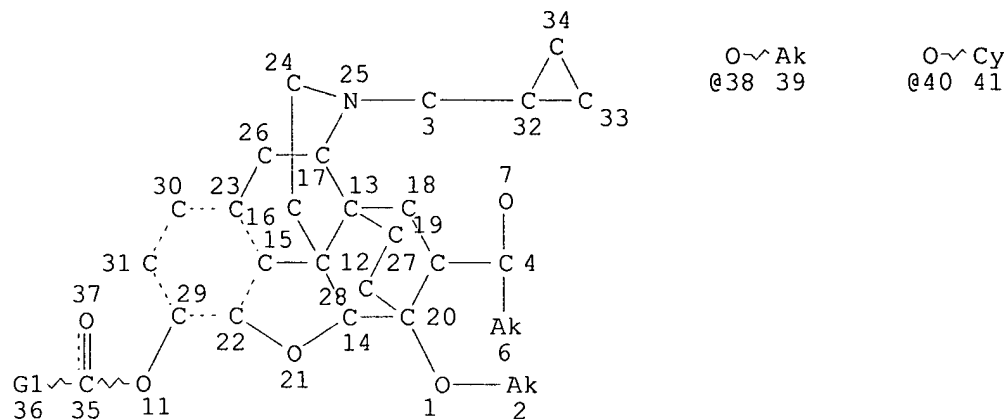
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<http://www.cas.org/ONLINE/UG/regprops.html>

FILE USPATFULL

FILE COVERS 1971 TO PATENT PUBLICATION DATE: 9 Feb 2006 (20060209/PD)
FILE LAST UPDATED: 9 Feb 2006 (20060209/ED)
HIGHEST GRANTED PATENT NUMBER: US6996845
HIGHEST APPLICATION PUBLICATION NUMBER: US2006031974
CA INDEXING IS CURRENT THROUGH 9 Feb 2006 (20060209/UPCA)
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 9 Feb 2006 (20060209/PD)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Dec 2005
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Dec 2005

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L10 STR



VAR G1=AK/CY/38/40

NODE ATTRIBUTES:

DEFAULT MLEVEL IS ATOM

DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:

RING(S) ARE ISOLATED OR EMBEDDED

NUMBER OF NODES IS 37

STEREO ATTRIBUTES: NONE

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